



Original Article

Liver Involvement by Perforated Peptic Ulcer: A Systematic Review

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Abstract

Background and Objective: Liver penetration by a confined perforation of peptic ulcer is a rare but severe event. Its clinical and pathological features are unclear. **Methods:** In total, 41 qualified English publications were identified using the PubMed database and one in-house case. **Results:** Among the 42 patients, 20 patients had liver involvement by a perforated duodenal ulcer and 22 by a gastric ulcer. Among the 23 cases of known ulcer histology, 2 ulcers were malignant and were adenocarcinomas in the gastric remnant and the remaining 21 ulcers were confirmed as histologically benign (for frequency of malignancy in duodenal versus gastric ulcers, $p = 0.48$). The presence of hepatocytes was the clue of diagnosis for 19 cases. The median ages of the patients were 64.5 years (95% Confidence Intervals [CI] 53.40–71.90) for duodenal ulcer and 65.5 years (95% CI: 59.23–70.95) for gastric ulcer, respectively. The male to female ratio was 1.5:1 for duodenal ulcers and 2:1 for gastric ulcers. Patients with liver involvement of a perforated gastric ulcer were more likely to have a larger ulcer (median largest dimension, 4.75 cm versus 2.5 cm, $p = 0.014$). Female patients with liver involvement of a gastric ulcer were older than male patients (median age 72 versus 60 years, $p = 0.045$). There were no differences in gender, region (Asia, Europe, America versus others), use of non-steroidal anti-inflammatory drugs ($n = 15$), *H. Pylori* positivity ($n = 10$), possible history of peptic ulcer disease ($n = 19$) or mortality ($n = 32$) between duodenal and gastric ulcers. **Conclusions:** Careful histologic examination, clinicopathological correlation, and immunohistochemistry are critical to establish the diagnosis and avoid misdiagnosing liver involvement as malignancy.

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Keywords: Duodenal ulcer; Gastric ulcer; Liver penetration; Peptic hepatitis.

Abbreviations: PUD, peptic ulcer disease; GIT, gastrointestinal tract; CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs; CT, computed tomography; MRI, magnetic resonance imaging.

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Introduction

The classic type of peptic ulcer perforation implies the acute rupture of the stomach or intestinal wall with an out-pouring of gastrointestinal contents and might result in focal or generalized peritonitis. By contrast, the confined perforation of a peptic ulcer is defined as the penetration into and confinement within the tissue of an adjacent structure or organ by peptic ulceration.¹ The most common organ involved in the confined perforation is pancreas, followed by gastrohepatic omentum, biliary tract, and liver.² Peptic ulcer penetration into the liver is a rare complication that is poorly understood.² Here we identified 41 cases in the English literature and an in-house case, aiming to characterize the clinical and histological features of this entity.

Materials and methods

Case identification and selection

We conducted a comprehensive literature search in PubMed in February 2021. We used the terms of "gastric ulcer AND perforation AND liver", "duodenal ulcer AND perforation AND liver", "peptic ulcer AND perforation AND liver", "gastric ulcer AND penetration AND liver", "duodenal ulcer AND penetration AND liver", "peptic ulcer AND penetration AND liver", "gastric cancer AND perforation AND liver", "gastric carcinoma AND perforation AND liver", "gastric carcinoma AND penetration AND liver", "gastric carcinoma AND perforation AND liver", "duodenal cancer AND perforation AND liver", "duodenal carcinoma AND perforation AND liver", "duodenal cancer AND penetration AND liver", "duodenal carcinoma AND penetration AND liver", and "duodenal carcinoma AND penetration AND liver". Only original articles were retrieved and reviewed. Additional cases were then identified through the review process. In addition, one in-house case was included.

A case would be selected and included in this study if: (1) it presented cases of gastric ulcer or duodenal ulcer penetration or perforation of the liver with a confirmed diagnosis; and (2) published in a peer-reviewed journal in English. All case selection was performed by author JJ.

Data extraction

The following data were extracted from original articles or

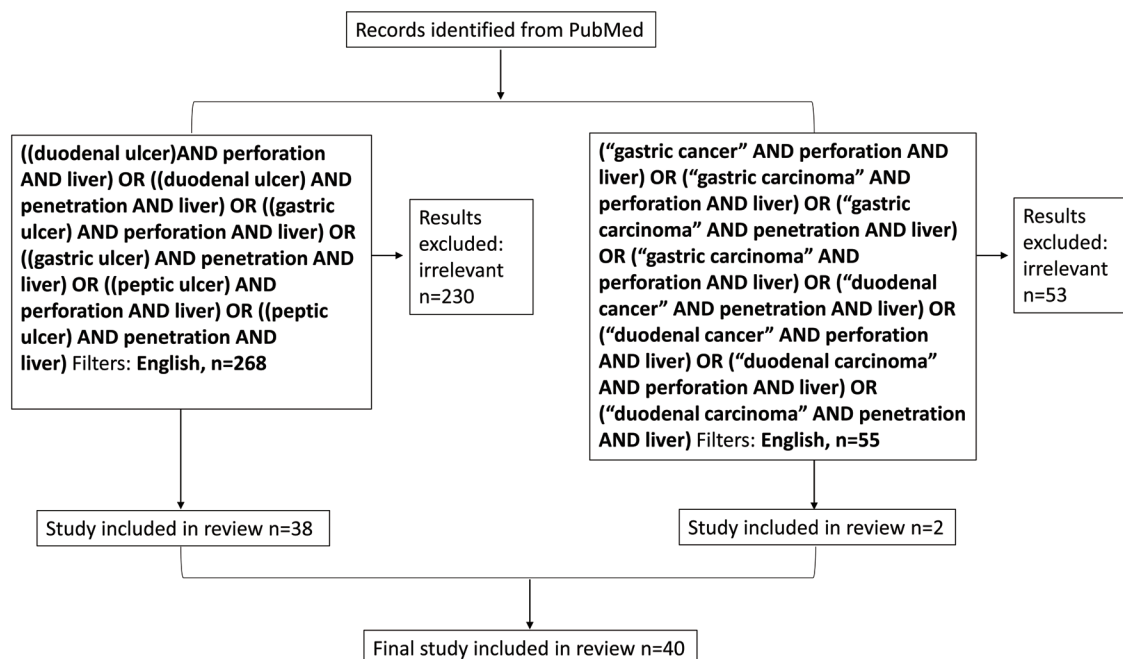


Fig. 1. Study flow diagram.

pathological report, if available: last name of the first author, publication year, country/region of the corresponding author, age, gender, location of the ulcer, clinical symptoms and signs, histology, endoscopic finding, imaging, ulcer size in largest dimension, laboratory results, outcome, and length of follow-up. All of the case entries were assessed by author JJ.

Statistical analysis

Demographic and clinical parameters were compared between duodenal ulcers and gastric ulcers or between males and females for duodenal ulcers or gastric ulcers using a two-tailed Student's t-test for continuous variables and Fisher exact or Chi-squared test for categorical variables as indicated. A p -value <0.05 was considered statistically significant. Confidence interval (CI) was calculated using t statistics.

Results

Case collection

Out of 323 articles identified from PubMed by a computerized search in February 2021, 40 publications that presented 41 patients with the liver involved with perforation or penetration of a duodenal or gastric ulcer were identified. With one additional incoming referral case of duodenal ulcer penetration into the liver found at the Princeton Medical Center, Plainsboro, NJ, 42 patients qualified and were included in this series (Fig. 1).

Clinical features

Among the 42 patients, 20 patients had liver involvement with a perforated duodenal ulcer and 22 patients had liver

involvement with a perforated gastric ulcer. Among the 23 cases with known ulcer histology, 2 were malignant and were adenocarcinomas in the gastric remnant,^{3,4} and the 21 remaining ulcers (11 duodenal and 10 gastric ulcers) were confirmed as histologically benign. However, the frequency of malignant ulcers was not different between duodenal and gastric ulcers ($p = 0.48$).

For duodenal ulcers, the distribution of patient age was from 21 to 88 years, with a mean of 62.65 and a median of 64.5 years (95% CI: 53.40–71.90). The mean age was 62.75 years for women (21–88 years, median 75 years, 95% CI: 40.77–84.73), and 62.58 years for men (27–85 years, median 60 years, 95% CI: 52.85–72.31) (Fig. 2a). The ratio of male versus female was 1.5:1 (male = 60% and female = 40%). The majority of the duodenal ulcers occurred in the first portion of the duodenum ($n = 17$), among which 10 cases were located in the anterior wall of the first portion (Fig. 3a). The leading symptom or sign was abdominal pain or tenderness ($n = 15$), followed by nausea/vomiting/anorexia ($n = 11$) and gastrointestinal tract (GIT) bleeding ($n = 8$). The most frequently noticed abnormal lab results were low red blood cell count or hemoglobin level ($n = 9$, 90%), followed by leukocytosis ($n = 7$, 78%) and elevated C-reactive protein ($n = 4$ (80%)). An abnormal liver function that was defined by elevated aminotransferase, bilirubin, alkaline phosphatase, gamma-glutamyltransferase and reduced albumin, occurred in 50% of duodenal ulcer patients ($n = 4$). Ten patients had information of possible non-steroidal anti-inflammatory drugs (NSAIDs) use with an equal distribution between with and without NSAIDs use ($n = 5$, for each). Four cases were positive for *H. pylori* infection and two were negative. One patient had a previous history of peptic ulcer disease (PUD) and five patients did not have a relevant history.

For gastric ulcers, the distribution of patient age was from 42 to 91 years, with a mean of 65.09 and a median of 65.5 years (95% CI: 59.23–70.95). Female patients were significantly older ($p = 0.045$) (Fig. 2b). The mean age was 73.29 years for women (55–91 years, median 72 years, 95% CI: 59.66–86.91), and 60.93 years for men (42–80

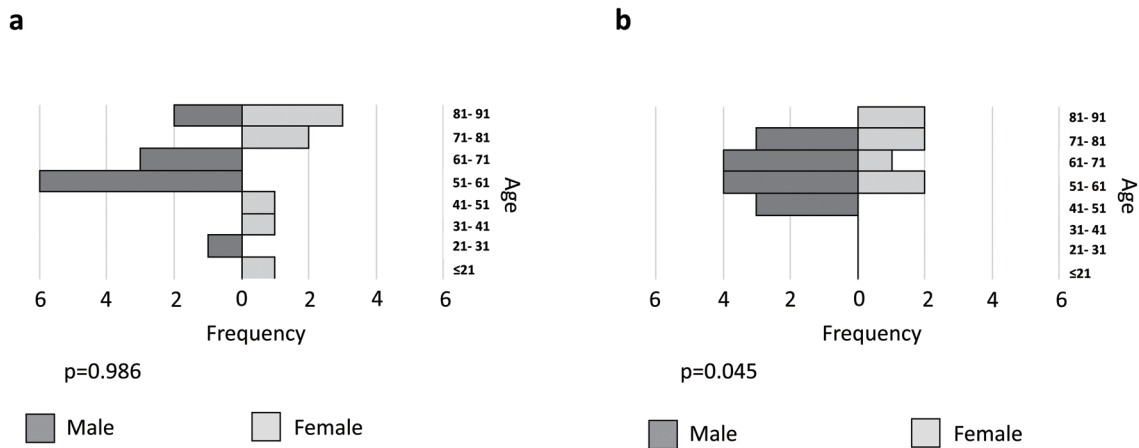


Fig. 2. Distribution of patients' age for: (a) duodenal ulcer; and (b) and gastric ulcer separated by gender. *p*-value: comparison between male and female patients by Student *t*-test.

years, median 60 years, 95% CI: 54.43–67.43). The ratio of male versus female was 2:1 (male = 66.7% and female = 33.3%). The majority of the gastric ulcers occurred in the antrum or pylori region ($n = 12$), followed by the gastric body ($n = 8$) (Fig. 3b). The leading symptom/sign was abdominal pain or tenderness ($n = 16$), followed by GIT bleeding ($n = 12$) and then nausea/vomiting/anorexia ($n = 8$). The most frequently noticed abnormal lab results were low red blood cell count or hemoglobin level ($n = 12$, 100%), followed by leukocytosis ($n = 10$, 91%), and elevated alkaline phosphatase ($n = 5$, 71%). Abnormal liver function occurred in 57% of gastric ulcer patients ($n = 8$). Two patients had possible NSAIDs use and three did not. Three cases were associated with *H. pylori* infection and one was not. Eight patients had a previous history of PUD and five patients did not have a relevant history.

The comparison of clinical and demographic characteristics of duodenal and gastric ulcers is given in Table 1. The size of gastric ulcers was significantly larger than duodenal ulcers (median largest dimension = 4.75 cm versus 2.5 cm, $p = 0.014$); however, all other features were not statistically different between the duodenal and gastric ulcers.

Gross manifestations

Under endoscope or during surgery, a large or giant ulcer (defined as the largest dimension of ≥ 3 cm for gastric ulcers⁵ and 2 cm for duodenal ulcer⁶) was described in 25 patients;^{7–31} A polypoid or pseudotumoral mass that protruded from the central area of the ulcer bed was mentioned frequently (in 11 cases^{8,9,13,14,21,24,32–36}). Five ulcers had an irregular margin.^{14,18,22,28,37} In addition, direct gross-examination of the liver tissue was possible under endoscopy.³⁸ One group recently reported a case of duodenal ulcer penetration into the previous hemihepatectomy site due to the detection of a ligature at the ulcer floor.¹¹ Thirteen cases were diagnosed by the direct observation of an ulcer that perforated into the liver during surgery.^{4,8,12,21,24,26,27,29,33,34,39,40}

Radiological manifestations

On radiological imaging, the connection between the stomach or duodenum and the liver was recorded in eight cas-

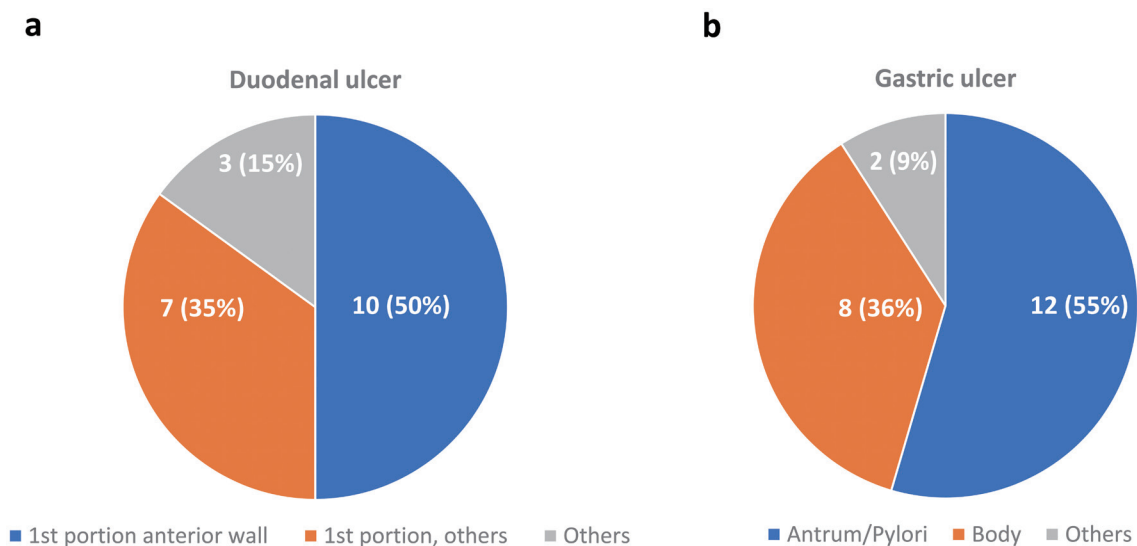


Fig. 3. Anatomical location of: (a) perforated duodenal ulcer; and (b) and gastric ulcer.

Table 1. Clinical and demographic features of duodenal and gastric ulcers with liver perforation or penetration. Data presented as median (quartile)

	Duodenal ulcer (n = 20)	Gastric ulcer (n = 22)	p-value
Age (years)	64.5 (54–81)	65.5 (53–73.5)	0.64
Ulcer histology			
Malignant/total	0/11	2/12 (16.7%)	0.48
Gender			
Female/total	8/20 (40%)	7/21 (33.3%)	0.66
Region			0.68
Asia	8 (40%)	7 (31.8%)	
Europe	6 (30%)	11 (50%)	
America	5 (25%)	3 (13.6%)	
Other	1 (5%)	1 (4.5%)	
History of NSAIDs use (n = 15)			0.99
yes	5 (50%)	2 (40%)	
no	5 (50%)	3 (60%)	
<i>H. Pylori</i> test (n = 10)			0.99
positive	4 (66.7%)	3 (75%)	
negative	2 (33.3%)	1 (25%)	
Possible history of PUD (n = 19)			0.14
yes	1 (16.7%)	8 (61.5%)	
no	5 (83.3%)	5 (38.5%)	
Size of ulcer (largest dimension cm) (n = 18)	2.5 (1.38–3.20)	4.75 (3.25–5.75)	0.01
Mortality (n = 32)			0.66
dead	2 (13.3%)	4 (23.5%)	
alive	13 (86.75)	13 (76.5%)	
Follow-up (days)	63 (41.25–225)	90 (54–570)	0.73

NSAIDs, non-steroidal anti-inflammatory drugs.

es,^{10,22,23,30,39,41–43} which were revealed by the observation of the movement of oral contrast or air bubbles between the two organs or fistula formation on computed tomography (CT), ultrasound or magnetic resonance imaging (MRI). Direct observation of an ulcer that penetrated the liver was observed or suspected in three cases, all by CT.^{16,17,36} By ultrasound, the target lesion was observed in two cases.^{14,28} Perforation of a stomach ulcer into the liver with an inflammatory change in the adjacent fat was demonstrated by CT by a brief report.¹⁷ Malignancy was radiologically suspected in two cases that included the in-house case.

Histological features

Among the 42 cases, histological features were available in 32 cases. The presence of hepatocyte in biopsy or cytology examination was the clue of diagnosis for 19 cases. Among them, the most frequently observed presentation was peptic hepatitis (hepatocyte with a surrounding inflammatory reaction), which was found in nine cases,^{10,13,18,22,25,28,31,35,37} and two cases did not have any apparent inflammation^{9,14} and no information of inflammation was mentioned in five cases.^{7,19,20,32,36} In the first article that described the features of peptic hepatitis, atypical hepatocytes were demonstrated.¹⁰ Other changes in the liver tissue at the site of

perforation were reported, which included macro-microvesicular degeneration, pseudoacinar transformation and perisinusoidal fibrosis,¹⁵ and fibrotic granulation tissue.¹⁶ Eight cases had concurrent liver abscess formation. In addition, one patient in the literature presented with a liver tumor at the site of perforation with an absence of hepatocytes at the gastric ulcer biopsy, which was further confirmed as a nodule of reactive inflammation with no sign of malignancy after surgery.³³ The in-house case was first diagnosed as malignancy (adenocarcinoma) in biopsy samples with the presence of atypia and cytoplasmic fat vacuoles that appeared to mimic signet ring cells but was later confirmed as a perforated duodenal ulcer that involved the liver (Fig. 4). The diagnostic pearls (Table 2) were the lobular configuration of large, atypical (hepatocytic) cells, lobular clusters of reactive biliary epithelium, and the CK8/18 and CK7 positive staining pattern of the reactive biliary epithelium. Of note, hepatoid adenocarcinoma of the stomach was positive for CDX-2 and hepatocellular carcinoma and reactive hepatic tissue were not.⁴⁴

Discussion

The incidence and prevalence of PUD decreased in recent decades, possibly due to the decrease in *H. pylori* infec-

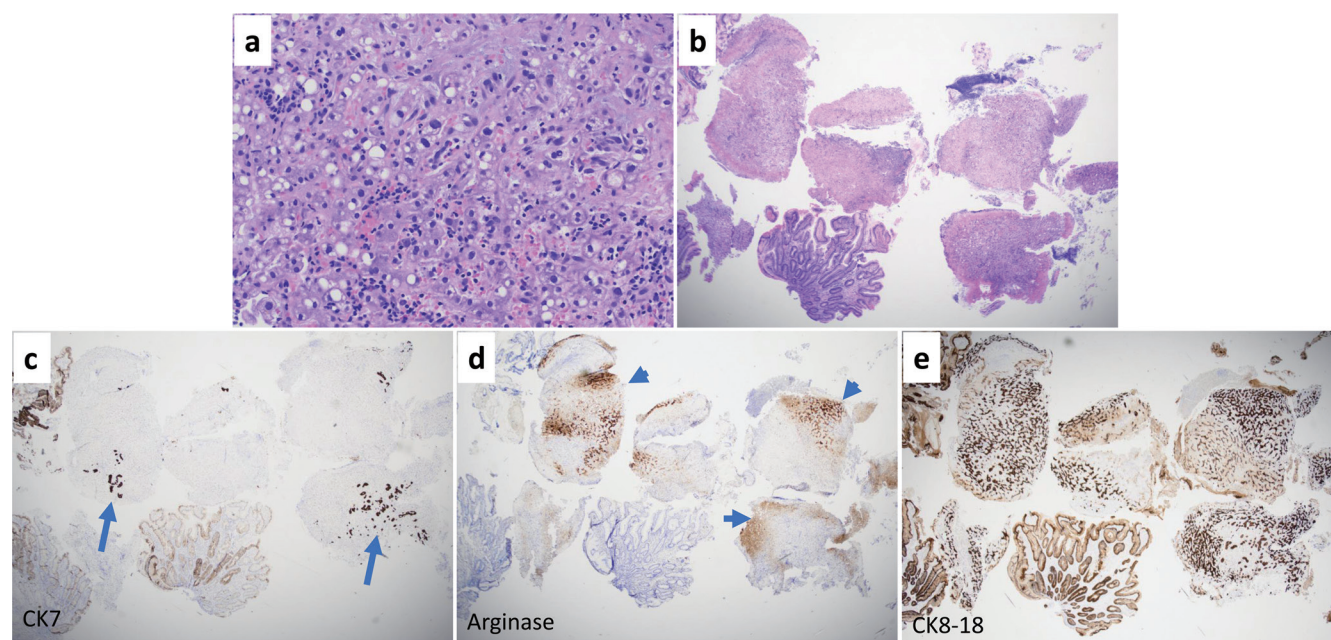


Fig. 4. Representative images of biopsy samples from a duodenal ulcer penetration that involved the liver by Hematoxylin & Eosin staining: (a) 200 \times ; (b) 40 \times ; (c) immunohistochemistry of CK7; (d) arginase; and (e) CK8/18. Biopsy samples showed hepatocyte with: (a) atypia, steatotic change, and inflammation; (b) infiltrating glands; (c) atypical epithelium was positive for CK7 and had a lobular configuration in low-power view (arrows); (d) involved liver parenchyma was positive for arginase (arrowheads); and (e) positive staining in CK8/18 suggestive of a biliary origin and CK8/18 might be confused with hepatoid carcinoma. The presence of biliary epithelium negated the possibility of a hepatoid carcinoma.

tion.⁴⁵ However, PUD complications, which include perforation, remain a substantial healthcare problem.⁴⁶ PUD perforation had a mortality rate of 5.7%–25%.^{47–49} In this systematic review, although peptic ulcer perforation/pen-

etration of the liver was a rare event, the mortality rate for duodenal and peptic ulcers were 13.3% and 23.5%, respectively. A better understanding of the disease entity might be warranted for better management of the condition and

Table 2. Diagnostic pearls for differential diagnosis of peptic ulcer with liver perforation or penetration versus hepatocellular carcinoma and hepatoid adenocarcinoma

	Peptic ulcer that involves liver	Hepatoid adeno-carcinoma	Hepatocellular carcinoma, metastatic
Clinical presentation	Some, but not all, with history of peptic ulcer; normal serum AFP	Elevated serum AFP	History of hepatocellular carcinoma; elevated serum AFP
Cytology	Biphasic atypical cells including reactive hepatocytes and bile ducts	Large, atypical cells with abundant eosinophilic cytoplasm (cytoplasmic glycogen and hyaline globules)	Similar to that in hepatoid adenocarcinoma
Histology	Lobular configuration of the atypical glands (bile ducts), and atypical large polygonal cells (hepatocytes); no bona fide single cells	Lack of small glands with cuboidal epithelium (bile ducts); infiltrative pattern; single cells may present	Similar to that in hepatoid adenocarcinoma
Immunohistochemistry			
positive	Hepatocytes are positive for CK8/18, arginase, HepPar1 and TTF-1 (cytoplasm) while bile ducts are positive for CK8/18 and CK7	Positive for CDX-2, HepPar1, AFP, Glypican 3, CEA and CK19	Positive for CK8/18, arginase, HepPar1, Glypican 3 and TTF-1 (cytoplasm);
Immunohistochemistry			
negative	Bile ducts are negative for arginase, HepPar1 and TTF-1 (cytoplasm) while hepatocytes are negative for CK7	Negative for CK7	Negative for CDX-2, CK19 (10%+), CK20 (10%+) and CK7

AFP, alpha-fetal protein; CK, cytokeratin; TTF-1, Thyroid transcription factor-1; CDX-2, Caudal Type Homeobox 2; CEA, carcinoembryonic antigen.

differential diagnoses.

Compared with the uncomplicated duodenal and gastric ulcers from literature, which had a mean age of 54.3 years (95% CI: 52.8–55.9) and 65.6 years (95% CI: 64.1–67.1),⁵⁰ patients with liver penetration due to duodenal ulcer were older, with a mean age of 62.65 years (95% CI: 53.40–71.90) and patients with liver penetration due to gastric ulcer had similar ages, with a mean age of 65.09 years (95% CI: 59.23–70.95). In this analysis of a broad range of publications (from 1880 to 2021), duodenal and gastric ulcers were male predominant, with a male to female ratio from 1.5:1 to 2:1. However, the male predominance in peptic disease has changed.⁵¹ There was approximately a three-fold increase in the percentage of women with perforated duodenal ulcer in the last 45 years.⁵² Recent publications showed that females accounted for more than half of the perforated duodenal and gastric ulcers.⁴⁹ This analysis showed females with perforated gastric ulcer were significantly older than males, which was consistent with previous reports.^{49,52}

Unlike the free perforation that has the hallmark presentation of the classic triad (sudden onset of abdominal pain, tachycardia, and abdominal rigidity), the presentation of peptic ulcers with liver penetration is largely non-specific with abdominal pain or tenderness being the most frequently reported symptoms or indications, and could be more obscure (e.g., dizziness and weakness²⁹). Abnormal liver function as defined by elevated aminotransferase, bilirubin, alkaline phosphatase, gamma-glutamyl transferase and reduced albumin, occurred in 50% of duodenal ulcers and 57% of gastric ulcers and most of the abnormality, especially the elevated aminotransferase, was mild to moderate, which might explain the local non-specific inflammation in the liver. However, the diagnostic value of liver function tests in cases of liver penetration might be limited. Of note, only 16.7% of perforated duodenal ulcers that involved the liver had a potential previous history of PUD. Although radiological studies might provide diagnostic hints, such as the target sign on ultrasound and the direct observation of a connection between the liver and alimentary tract, endoscopic examination and biopsy played critical roles in establishing the diagnosis and excluding malignancy. Different histological features of the perforation site (inflammation, granulation tissue, fibrosis, and liver abscess) might be determined by the duration of the perforation. With sudden inflammation, liver cells might show atypical features that resemble a carcinoma as first described by Guerrieri *et al.* in 1987¹⁰ and the in-house case. Endoscopically, penetration into the liver could frequently appear as a polypoid or pseudotumoral mass that protruded from the central area of the ulcer bed.^{8,9,13,14,21,24,32–36} This feature, combined with the irregular ulcer ground and margin, the giant ulcer size (average size 5.1 cm for gastric ulcers and 2.4 cm for duodenal ulcers) and clinical features (weight loss and emaciation) always raised the potential for malignancy. However, as indicated by Padda *et al.*,²⁴ an endoscopic biopsy had the potential risk of inducing active bleeding. For cases that probably require surgical management endoscopic biopsy might be unnecessary.²⁴ A potential iatrogenic free perforation often occurred after endoscopic air inflation, as shown by two case reports included in this analysis.^{19,36}

The limitations of this study include the small sample size and the quality of the case reports, despite being the first systematic review. The risk factors that predisposed for perforation include the use of NSAIDs (including aspirin), smoking and *H. Pylori* infection.^{46,53,54} However, among the 42 patients, only 15 had information available on NSAIDs usage and 10 for *H. Pylori* test results. With a significant amount of missing data, it was difficult to evaluate the risk factors associated with confined peptic ulcer liver perforation or penetration. Therefore, caution should be used when

interpreting and applying the related findings.

Conclusions

We summarized the clinical, demographic and histological features of liver involvement by perforated peptic ulcers. Histology examination, either by endoscopic biopsy or by surgical pathology, are required to make the diagnosis. Clinico-pathological correlation and immunohistochemistry are also critical to avoid misdiagnosing liver involvement as malignancy. However, the associated risk factors require further investigation.

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Conflict of interest

The authors have nothing to disclose.

Author contributions

Study concept and design (LZ), acquisition of data (JJ), analysis and interpretation of data (LZ, JJ), drafting of the manuscript (JJ), critical revision of the manuscript for important intellectual content (LZ, JJ), administrative, technical, or material support, study supervision (LZ).

Data sharing statement

No additional data are available.

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